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Inherited *MC1R* variants in patients with melanoma are associated with better survival in women

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Summary

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Conflicts of interest

None declared.

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Background Women have a better melanoma prognosis, and fairer skin/hair colour. The presence of inherited *MC1R* variants has been associated with a better melanoma prognosis, but its interaction with sex is unknown.

Objectives To evaluate the relationship between germline *MC1R* status and survival, and determine any association with sex.

Methods This was a cohort study including 1341 patients with melanoma from the Melanoma Unit of the Hospital Clinic of Barcelona, between January 1996 and April 2018. We examined known sex-related prognosis factors as they relate to features of melanoma and evaluated the sex-specific role of *MC1R* in overall and melanoma-specific survival. Hazard ratios (HRs) were calculated using univariate and multivariate Cox logistic regression.

Results Men showed lower overall survival than women ($P < 0.001$) and the presence of inherited *MC1R* variants was not associated with better survival in our cohort. However, in women the presence of *MC1R* variants was associated with better overall survival in the multivariate analysis [HR 0.57, 95% confidence interval (CI) 0.38–0.85; $P = 0.006$] but not in men [HR 1.26, 95% CI 0.89–1.79; $P = 0.185$ (P -value for interaction 0.004)]. Analysis performed for melanoma-specific survival showed the same level of significance.

Conclusions Inherited *MC1R* variants are associated with improved overall survival in women with melanoma but not in men. Intrinsic sex-dependent features can modify the role of specific genes in melanoma prognosis. We believe that survival studies of patients with melanoma should include analysis by sex and *MC1R* genotype.

What's already known about this topic?

- Inherited *MC1R* variants have been associated with a better melanoma prognosis, but their interaction with sex is unknown.

What does this study add?

- *MC1R* variants are related to better overall survival and melanoma-specific survival in women but not in men.

What is the translational message?

- These differences between the sexes could imply future changes in melanoma follow-up and treatment strategies.
- This provides a basis for understanding the interaction between sex-related genes and germline variants in cancer.

Melanoma is the most aggressive of the common skin malignancies and is responsible for 75% of deaths from skin cancer.¹ The American Joint Committee of Cancer staging system gives a clear prognostic value for patients with melanoma but cannot explain individual differences in survival.²

Femaleness has been demonstrated to be an independent, favourable prognostic factor in cutaneous malignant melanoma across nearly all tumour stages, including thin invasive tumours and advanced melanomas.^{3–7} Furthermore, males exhibit worse prognostic features, as they are more likely to have thick or ulcerated melanomas, and melanoma located on the trunk.^{7–9} Moreover, recent data highlight differences in body mass index and interferon regulation between men and women that may differently affect antitumour responses to immunotherapy.^{10,11}

Women have a higher prevalence of lighter hair colour and fairer skin than men.^{12,13} The interaction between sex and genetic variants associated with tanning facility has been reported recently.¹⁴

MC1R is a highly polymorphic gene in the white population and one of the most important regulator genes in human skin and hair pigmentation.^{15–17} MC1R variants have been classified as 'r' variants when they have a low association with red hair colour phenotype (RHC) and 'R' variants when they are highly associated with RHC.^{18–20} Interestingly, R variants have been associated with fairer skin phenotypes in women.²¹ Finally, inherited MC1R variants increase the risk of developing a primary melanoma,²² yet appear to provide a survival advantage to these individuals.^{23–25}

We hypothesized that inherited MC1R variants could play a differential role in survival in women and men.

Materials and methods

Cohort description

We used a cohort study design to analyse the prognostic value of germline MC1R status depending on sex in patients with melanoma. The cohort included 1341 consecutive patients with melanoma who were prospectively followed-up in the Melanoma Unit of Hospital Clinic of Barcelona, between January 1996 and April 2018. All patients gave their written informed consent according to the Declaration of Helsinki, and the study was approved by the Research Ethics Committee of the Hospital Clinic of Barcelona (HCB/2015/0298 and HCB/2015/1032).

Clinical and phenotypic data from the patients and melanoma characteristics were collected in the Melanoma Unit database. For this study we extracted the basal demographic characteristics of the patients, clinical and pathological melanoma features, and survival outcome.

As inclusion criteria, only patients with a histopathological diagnosis of an invasive primary melanoma were considered for the study. For patients with multiple melanomas, the most

invasive melanoma tumour by Breslow thickness was included, as it is the one that drives the prognosis.

Sentinel lymph node biopsy and follow-up protocols were carried out according to the institution's guidelines.^{26,27} Overall survival (OS) time was calculated from the date of diagnosis of the primary melanoma to the date of death by any cause or last follow-up visit. Melanoma-specific survival (MSS) was calculated from the time of diagnosis of the primary melanoma to the time of death by melanoma or the last follow-up visit.

Our study was performed at a well-known referral centre for advanced cases of melanoma, but bias may exist as it was a single-centre study.

MC1R molecular screening

Genomic DNA was extracted from peripheral blood lymphocytes or saliva by standard methods. The whole coding region of MC1R was sequenced as reported elsewhere.²⁸

Nonsynonymous MC1R variants were classified as RHC ('R') or non-RHC ('r') according to previously reported criteria.^{20,23,28} Therefore, the p.D84E, p.R142H, p.R151C, p.I155T, p.R160W and p.D294H MC1R variants were classified as 'R', while all the other nonsynonymous MC1R variants were classified as 'r'. Synonymous variants were considered as wild-type (WT) MC1R alleles ('w'). According to this classification we determined the following genotypes: R/R, R/r, R/w, r/r, r/w, w/w.

Statistical analyses

Pearson's χ^2 -test, trend test for ordinal variables and the Kruskal–Wallis rank sum test were used to compare categorical, ordinal and continuous variables, respectively. Survival curves based on Kaplan–Meier methods were used to calculate survival outcomes and the log-rank test was used for curve comparison.

We considered OS and MSS as the main variables. In order to better manage possible statistical multiplicity when considering two primary variables (OS and MSS), P-values were considered statistically significant if $P \leq 0.025$, following Bonferroni correction. If the described model produced probability values that reached significance, the following hierarchical stepwise process to reject the null hypotheses was followed: the interaction effect with sex was evaluated and, if this was significant at $P < 0.10$ (the usual cut-off for interaction effects), the analysis was stratified by sex.^{29,30}

Furthermore, in the stratified analysis, univariate and multivariate Cox logistic regression analysis were performed to assess the influence of germline MC1R status in OS and MSS depending on sex, and to estimate the hazard ratio (HR) for each of the survival outcomes.

Statistical analyses were performed using the computing environment R and RStudio.^{31,32}

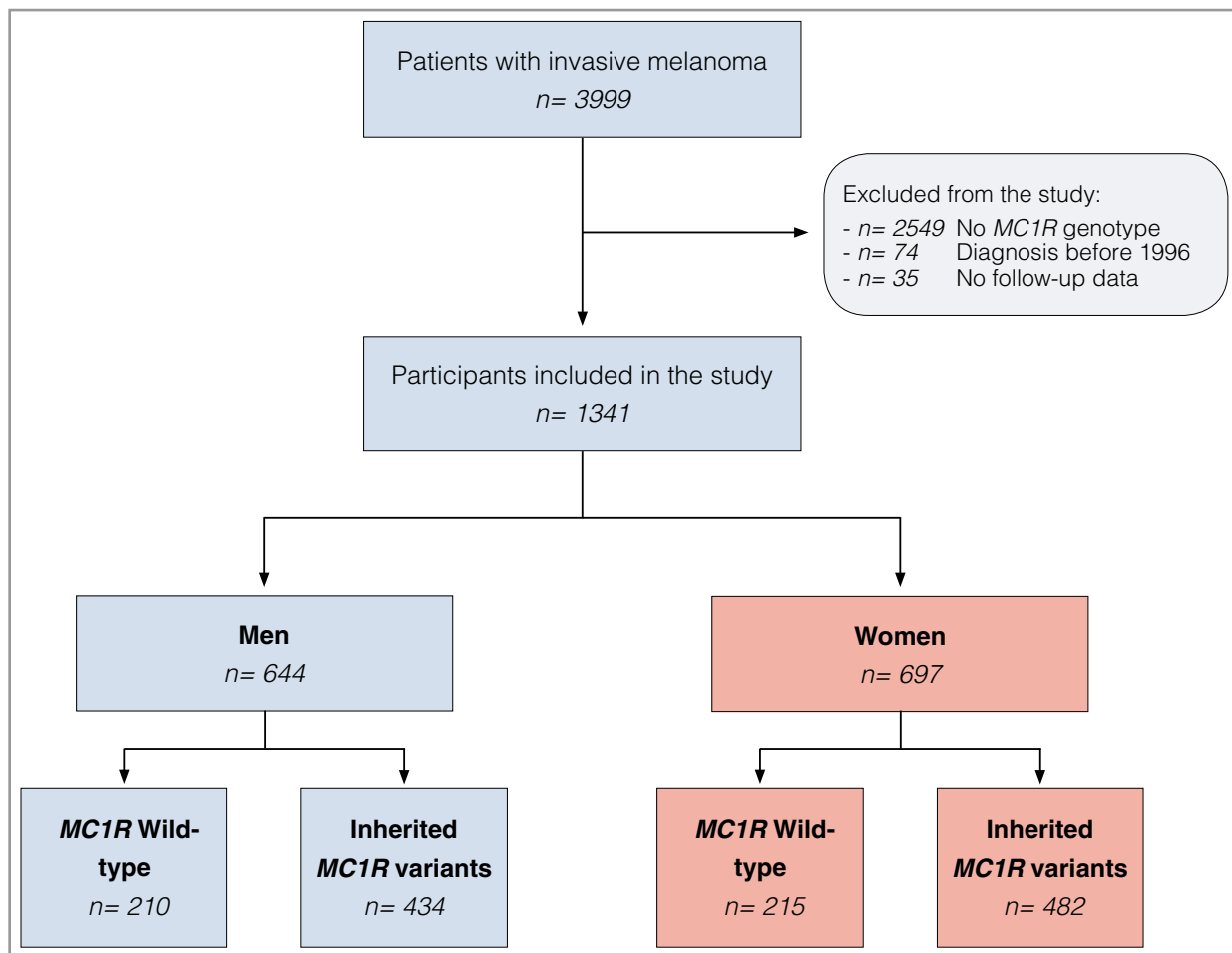


Fig 1. Flowchart of the study cohort.

Results

A total of 3999 patients with a histopathological diagnosis of an invasive primary melanoma were identified. However, after applying the inclusion and exclusion criteria, 2658 patients were excluded, leaving 1341 eligible for inclusion (Fig. 1). Total person-months were 105 775 with an incidence rate of relapse of 2.72 cases per 1000 person-months. Median follow-up time was 63.5 months (interquartile range 31.5–115.9).

The demographic, clinical and genetic characteristics of all included individuals are summarized in Table 1, and the clinicopathological characteristics of all tumours are given in Table 2. The average age of onset was 52.2 years in women and 56.7 years in men, and the mean Breslow thickness was 2.1 mm and 2.5 mm, respectively. Phenotypic characteristics showed a predominance of white skin, phototypes II and III, brown eyes and brown hair. Women had thinner tumours, which were less often ulcerated than those in men. Women presented more often with superficial spreading melanomas and tumours on the lower extremities. Men presented more often with nodular melanomas and tumours on the trunk.

Considering that Breslow thickness and ulceration are two of the main prognostic factors in melanoma, we evaluated the association of *MC1R* genotype with these variables in our cohort. We saw no significant differences between *MC1R* WT individuals and *MC1R* variant carriers regarding Breslow index ($P = 0.908$). Similarly, no significant differences were detected between *MC1R* WT and *MC1R* variant carriers when stratified by ulceration ($P = 0.309$) (Table S1; see Supporting Information). Interestingly, the analysis was not statistically significant when stratified for female sex (Breslow index $P = 0.895$; ulceration $P = 0.925$).

Kaplan–Meier curves showed that men had lower OS rates than women ($P < 0.001$; Fig. 2). This worse prognosis in men was further confirmed in the analysis using the multivariate Cox logistic regression model [HR 1.48, 95% confidence interval (CI) 1.15–1.91; $P = 0.002$].

Analysis stratified by sex and *MC1R* genotype

Kaplan–Meier curves were modelled for patients with *MC1R* status. We did not detect statistically significant differences in

Table 1 Demographic, clinical and genetic characteristics of patients included at baseline

	Women (n = 697)	Men (n = 644)	Total (n = 1341)	P-value
Mean \pm SD age of onset (y)	52.22 \pm 18.12	56.68 \pm 16.58	54.37 \pm 17.53	< 0.001
Eye colour				< 0.001
Brown	355 (56.5)	335 (58.6)	690 (57.5)	
Green	160 (25.5)	81 (14.2)	241 (20.1)	
Blue	98 (15.6)	138 (24.1)	236 (19.7)	
Black	13 (2.1)	11 (1.9)	24 (2.0)	
Other	2 (0.3)	7 (1.2)	9 (0.8)	
Missing	69	72	141	
Hair colour				< 0.001
Brown	419 (66.9)	328 (57.5)	747 (62.5)	
Black	29 (4.6)	64 (11.2)	93 (7.8)	
Blonde	138 (22.0)	150 (26.3)	288 (24.1)	
Red	40 (6.4)	28 (4.9)	68 (5.7)	
Missing	71	74	145	
Ethnicity				0.620
White	629 (99.5)	574 (99.3)	1203 (99.4)	
Latin	1 (0.2)	2 (0.3)	3 (0.2)	
Asian	0 (0.0)	1 (0.2)	1 (0.1)	
Black	0 (0.0)	0 (0.0)	0 (0.0)	
Other	2 (0.3)	1 (0.2)	3 (0.2)	
Missing	65	66	131	
Phototype				0.760
I	42 (6.6)	40 (6.8)	82 (6.7)	
II	328 (51.3)	301 (51.5)	629 (51.4)	
III	228 (35.7)	210 (35.9)	438 (35.8)	
IV	40 (6.3)	33 (5.6)	73 (6.0)	
V	1 (0.2)	1 (0.2)	2 (0.2)	
Missing	58	59	117	
Naevus count				0.919
0–50	307 (54.0)	282 (53.6)	589 (53.8)	
51–100	149 (26.2)	143 (27.2)	292 (26.7)	
\geq 101	113 (19.9)	101 (19.2)	214 (19.5)	
Missing	128	118	246	
Number of melanomas				0.036
Single	549 (78.8)	476 (73.9)	1025 (76.4)	
Multiple	148 (21.2)	168 (26.1)	316 (23.6)	
MC1R status				0.488
Wild-type	215 (30.8)	210 (32.6)	425 (31.7)	
Variants	482 (69.2)	434 (67.4)	916 (68.3)	
MC1R genotype				0.245
RR	34 (4.9)	31 (4.8)	65 (4.8)	
Rr	80 (11.5)	51 (7.9)	131 (9.8)	
Rw	116 (16.6)	121 (18.8)	237 (17.7)	
rr	58 (8.3)	44 (6.8)	102 (7.6)	
rw	194 (27.8)	187 (29.0)	381 (28.4)	
ww	215 (30.8)	210 (32.6)	425 (31.7)	

Data are n (%) unless otherwise indicated.

OS between MC1R WT patients and carriers of any MC1R variant ($P = 0.24$; Fig. 3). Multivariate Cox regression analysis adjusted by sex, age, Breslow index and ulceration showed that MC1R genotype was not associated with better prognosis in this cohort (HR 0.88, 95% CI 0.68–1.14; $P = 0.349$).

We subsequently analysed the influence of sex on the effect of MC1R variants in survival. Kaplan–Meier curves showed that women with inherited MC1R variants had a better melanoma

prognosis than those with MC1R WT ($P < 0.007$). In contrast, the protective effect of inherited MC1R variants was not found in men ($P = 0.35$; Fig. 3).

Subsequently, we evaluated the interaction effect of sex and MC1R status for OS (P -value for interaction 0.004) and for MSS (P -value for interaction 0.052), which were in both cases statistically significant at alpha ($P < 0.10$), the usual measure of statistical significance for interaction effect. Consequently,

Table 2 Clinicopathological characteristics of the included tumours

	Women (n = 697)	Men (n = 644)	Total (n = 1341)	P-value
Mean \pm SD Breslow index	2.10 \pm 3.27	2.47 \pm 2.81	2.28 \pm 3.06	< 0.001
Ulceration				< 0.001
Absent	508 (80.6)	437 (72.2)	945 (76.5)	
Present	122 (19.4)	168 (27.8)	290 (23.5)	
Missing	67	39	106	
Mean \pm SD mitotic index	2.18 \pm 3.95	2.53 \pm 4.59	2.35 \pm 4.28	0.122
Missing	133	106	239	
Location				< 0.001
Trunk	248 (38.2)	330 (54.1)	578 (45.9)	
Lower limbs	184 (28.3)	78 (12.8)	262 (20.8)	
Head and neck	69 (10.6)	95 (15.6)	164 (13.0)	
Upper limbs	78 (12.0)	54 (8.9)	132 (10.5)	
Acral	50 (7.7)	48 (7.9)	98 (7.8)	
Mucosa	18 (2.8)	5 (0.8)	23 (1.8)	
Other	3 (0.5)	0 (0.0)	3 (0.2)	
Missing	47	34	81	
Histological subtype				0.003
Superficial spreading	459 (66.8)	397 (62.5)	856 (64.8)	
Nodular	99 (14.4)	105 (16.5)	204 (15.4)	
Acral lentiginous	33 (4.8)	45 (7.1)	78 (5.9)	
Lentiginous malignant	27 (3.9)	46 (7.2)	73 (5.5)	
Other	69 (10.0)	42 (6.6)	111 (8.4)	
Missing	10	9	19	

Data are n (%) unless otherwise indicated.

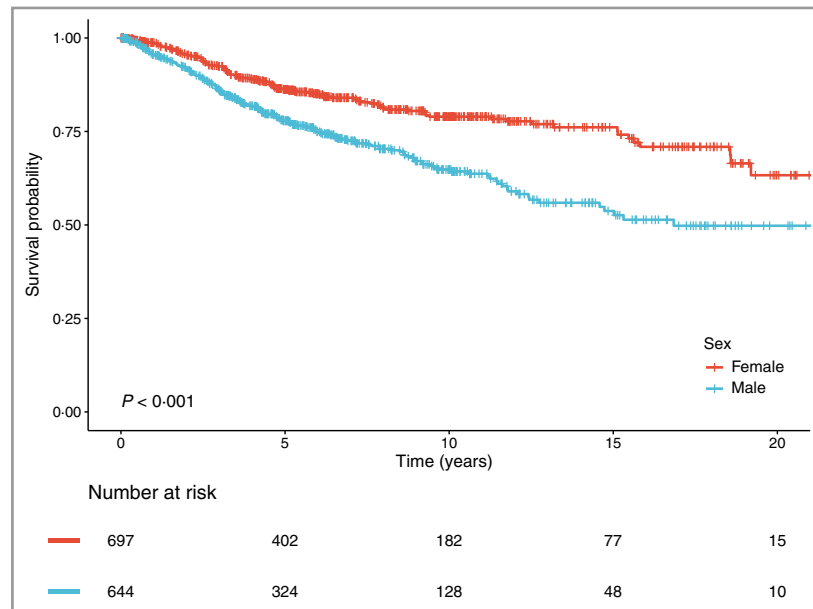


Fig 2. Overall survival by sex.

we observed that the survival benefit derived from the MC1R mutational status depends on the sex of the patients.

Univariate Cox logistic regression analysis of OS and MSS in women showed that later age at onset, thicker tumours, high mitotic index and tumour ulceration were associated with a worse prognosis. By contrast, total naevus count > 50 and the presence of inherited MC1R variants were protective.

Multivariate Cox logistic regression analysis including 630 women confirmed that the presence of inherited MC1R variants was a protective factor for OS (HR 0.57, 95% CI 0.38–0.85; $P = 0.006$) and MSS (HR 0.49, 95% CI 0.29–0.81; $P = 0.005$) (Table 3). After adjustment for other baseline characteristics (mitotic index, histological subtype and body site of the primary melanoma) the presence of any MC1R variation

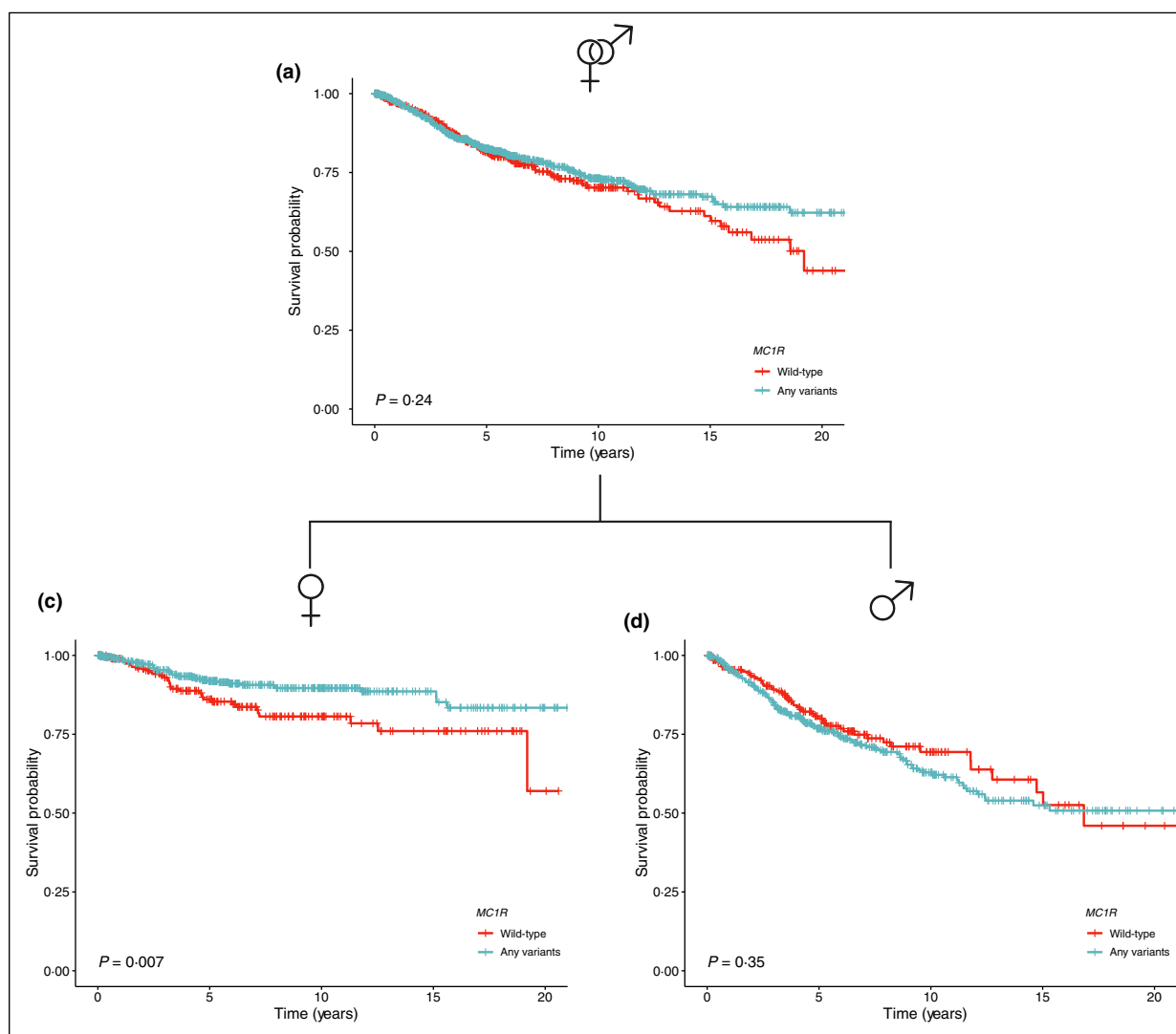


Fig 3. Overall survival by MC1R status depending on sex.

consistently showed a sizeable and statistical significance in HR estimation for OS and MSS.

Similarly, univariate Cox logistic regression analysis in men showed that later age at onset, thicker tumours, the presence of ulceration and a high mitotic index were mortal risk factors, and a naevus total count > 50 was a protective factor. Contrary to women, the presence of inherited MC1R variants was not associated with improved survival in men. Multivariate Cox logistic regression analysis including 605 men showed no effects on OS (HR 1.26, 95% CI 0.89–1.79; $P = 0.185$) or MSS (HR 1.09, 95% CI 0.71–1.67; $P = 0.685$) (Table 4).

Discussion

The significance of sex difference on melanoma prognosis is well known. Better MSS in women has been attributed to both lifestyle and biological factors. Women perform self-examination or tend to contact dermatologists for screening more

often than men, allowing an earlier diagnosis of melanoma in women.³³ Moreover, the survival prognosis is higher in women than in men throughout childbearing age, except during pregnancy. However, this survival benefit is not maintained after menopause. This suggests the importance of hormonal signalling in melanoma development.^{34–36}

A BioGenoMEL collaborative study suggested that the presence of any inherited MC1R variants was associated with improved melanoma survival, adjusting for age and sex (HR 0.82, 95% CI 0.66–1.02; $P = 0.08$).²³ The result only reached statistical significance with the addition of the Leeds cohort data (HR 0.77, 95% CI 0.64–0.93; $P = 0.005$).²³ Taylor *et al.* also suggested that the presence of MC1R variants is associated with better MSS (but not OS) in individuals with a first incident primary melanoma.²⁵ These analyses did not stratify by sex and, consequently, this putative protective effect in women was not evaluated.

In our study we identified that inherited MC1R variants are associated with better survival in women but not in men.

Table 3 Univariate and multivariate Cox regression analysis of overall survival (OS) and melanoma-specific survival (MSS) in women

	OS		MSS	
	Univariable [HR (95% CI, P-value)]	Multivariable [HR (95% CI, P-value)] ^a	Univariable [HR (95% CI, P-value)]	Multivariable [HR (95% CI, P-value)] ^b
Inherited MC1R variants (yes)	0.57 (0.39–0.83, 0.003)	0.57 (0.38–0.85, 0.006)	0.53 (0.34–0.85, 0.008)	0.49 (0.29–0.81, 0.005)
Age (continuous)	1.06 (1.05–1.08, < 0.001)	1.06 (1.05–1.08, < 0.001)	1.04 (1.03–1.06, < 0.001)	1.04 (1.02–1.05, < 0.001)
Breslow index (continuous)	1.06 (1.04–1.08, < 0.001)	1.04 (1.01–1.06, 0.006)	1.06 (1.04–1.08, < 0.001)	1.03 (1.00–1.07, 0.027)
Ulceration (present)	3.71 (2.48–5.56, < 0.001)	1.96 (1.27–3.01, 0.002)	4.83 (2.92–8.00, < 0.001)	3.02 (1.76–5.18, < 0.001)
Mitotic index (continuous)	1.09 (1.06–1.13, < 0.001)	–	1.12 (1.08–1.16, < 0.001)	–
Naevus total count (< 50)	–	–	–	–
51–100	0.52 (0.29–0.92, 0.026)	–	0.73 (0.38–1.39, 0.335)	–
≥ 101	0.41 (0.21–0.81, 0.010)	–	0.47 (0.21–1.07, 0.072)	–

HR, hazard ratio; CI, confidence interval. ^aMultivariable analysis based on 630 women and 101 events (C-index = 0.784); ^bMultivariable analysis based on 630 women and 63 events (C-index = 0.777)

Table 4 Univariate and multivariate Cox regression analysis of overall survival (OS) and melanoma-specific survival (MSS) in men

	OS		MSS	
	Univariable [HR (95% CI, P-value)]	Multivariable [HR (95% CI, P-value)] ^a	Univariable [HR (95% CI, P-value)]	Multivariable [HR (95% CI, P-value)] ^b
Inherited MC1R variants (yes)	1.17 (0.84–1.63, 0.347)	1.26 (0.89–1.79, 0.185)	0.98 (0.65–1.47, 0.917)	1.09 (0.71–1.67, 0.685)
Age (continuous)	1.05 (1.04–1.06, < 0.001)	1.04 (1.03–1.05, < 0.001)	1.02 (1.01–1.03, 0.001)	1.02 (1.00–1.03, 0.011)
Breslow index (continuous)	1.18 (1.14–1.22, < 0.001)	1.15 (1.10–1.20, < 0.001)	1.21 (1.17–1.25, < 0.001)	1.17 (1.12–1.23, < 0.001)
Ulceration (present)	2.75 (2.02–3.75, < 0.001)	1.41 (0.97–2.06, 0.074)	3.55 (2.40–5.25, < 0.001)	1.80 (1.13–2.88, 0.013)
Mitotic index (continuous)	1.06 (1.03–1.08, < 0.001)	–	1.08 (1.05–1.11, < 0.001)	–
Naevus total count (< 50)	–	–	–	–
51–100	0.47 (0.28–0.77, 0.003)	–	0.49 (0.26–0.93, 0.030)	–
≥ 101	0.65 (0.40–1.06, 0.086)	–	0.59 (0.30–1.15, 0.119)	–

HR, hazard ratio; CI, confidence interval. ^aMultivariable analysis based on 605 men and 165 events (C-index = 0.758). ^bMultivariable analysis based on 605 men and 103 events (C-index = 0.758)

Additionally, we did not observe more severe pathological tumour characteristics in women with MC1R variants. Therefore, our study indicates, for the first time, that the presence of inherited MC1R variants may be an independent protective factor in the survival of female patients with melanoma. Although the sex-related biological mechanisms that underlie this finding are unknown, we hypothesize that the regulation of oxidative stress could offer a partial explanation. In melanocytes, the loss of melanocortin 1 receptor (MC1R) function reduces DNA repair capacity and decreases antioxidant response,³⁷ causing genomic instability and increasing oxidative stress.³⁸ This may lead melanocytes to undergo malignant transformation. Interestingly, oestrogen (the primary female sex hormone) induces the generation of reactive oxidative species (ROS).³⁹ This fact is consistent with the higher incidence of melanoma in adult premenopausal women.⁴⁰ The effect of

ROS on malignant cell transformation is dose dependent. While certain levels of ROS promote malignant transformation, excessively high ROS levels cause detrimental oxidative stress that can lead to cell death.⁴¹ Therefore, we suggest that in women melanocytes harbouring MC1R variants could cause excessive oxidative damage that is detrimental to melanoma progression.

Previous studies have indicated that inherited MC1R variants contribute differently to pigmentation phenotype in men and women. Moreover, women carrying RHC MC1R variants tended to exhibit significantly fairer phototypes than men with the same MC1R genotypes.⁴² Differences between the sexes according to MC1R status do not only affect pigmentation phenotype. A recently published study has shown that the risk of developing melanoma associated with inherited MC1R variants is much higher in women than in men.⁴³ In the same line, several

studies have identified a sex-differential effect of MC1R on analgesic response.^{21,44} Specifically, women with two inherited MC1R variants show greater analgesia than men.⁴⁴ Taken together, these findings highlight the fact that MC1R is a pleiotropic protein involved in the regulation of different biological processes and show that some of these MC1R effects are sex dependent.

In conclusion, our results show that the presence of inherited MC1R variants improves survival in women with melanoma. This could explain some of the prognostic differences between men and women. Future prospective studies should take into account sex differences in survival and could help to explain how the inherited MC1R variants may play a role in survival. This could imply an improvement in personalized melanoma follow-up.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Analysis of clinicopathological characteristics according to MC1R genotype.